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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
FOLEY, SHANON A

ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/521,524	DAVIDSON ET AL.	
	Examiner	Art Unit	
	Shanon Foley	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 March 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-8 and 10-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-8 and 10-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant has amended claims 11, 15, 16, 17 and 22. Claims 2-8 and 10-25 are under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-8 and 10-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

Claims 11 and 16 remain vague and indefinite because the transitional phrase "consisting essentially" of does not define the metes and bounds of what is specifically to be excluded or what would be considered to materially alter the plasmids in the claims. Further confusion concerning the metes and bounds of what is to be specifically excluded is augmented by dependent claims 8, 10, 14, and 15, in which the backbone plasmids are "further comprising" certain ingredients and subsequence claims 17 and 22, in which both the shuttle and the backbone plasmids "comprise" other ingredients. The additional components in subsequent claims, such as incorporation of a gene of interest, substitutions, additions, deletions of E3, E4, and pIX regions, addition HSV Amplicon sequences, and addition of other sequences that allow integration into the host cell, also materially affect the plasmid compositions. Therefore, since it cannot be determined what is excluded or included from the claim language "consisting essentially of". This rejection affects all dependent claims 2-8, 10 and 12-15.

The actual components of the shuttle plasmid of claim 11 are also vague and indefinite because it cannot be determined point in time in which the plasmid lacks the loxP sequence and subsequently "consists essentially of" the specific map units recited.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection maintained for reasons of record.

The claims are drawn to a cloning system and a method for making recombinant adenovirus comprising an adenovirus backbone plasmid "consisting essentially of" an adenovirus genome lacking specific map units and a shuttle plasmid "consisting essentially of" certain map units. The claims do not appear to specifically exclude any other ingredients or coding sequences that would also materially affect the individual components and it is not clear what is to be materially excluded that would alter the invention while other added components would not. There is no definition in the specification that would differentiate what is considered to be materially altering to the skilled artisan.

Claims 2-8 and 10-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 2-8 and 10-25 recite that the backbone and the shuttle plasmids lack a loxP sequence. This negative limitation cannot be found in the original disclosure. The courts have found that any negative limitation or exclusionary proviso must have basis in the original disclosure. The mere absence of a positive recitation is not basis for an exclusion. See *Ex parte Grasselli*, 231 USPQ 393 (Bd. App. 1983), *aff'd mem.*, 738 F.2d 453 (Fed. Cir. 1984).

In response to the new matter and written description rejections, applicant argues that the lack of literal support is not enough and that the test is whether the disclosure reasonably conveys possession of the claimed invention to one skilled in the art and that the content of the drawings are also considered in determining compliance with the written description requirement. Applicant cites *In re Kaslow* and *Eiselstein v. Frank* for support. Applicant dismisses the support for the rejection provided by *Ex Parte Grasselli* in the previous action because the case is only two pages long and the court does not offer comparative analysis of the new concepts that violate the written description requirements. Applicant cites and summarizes *In re Wright* and argues that the added negative limitation to the claims in the instant case is similar to the circumstances in the case law. Applicant asserts that even though there is no *ipsis verbis* support in the instant application for the negative limitation, one skilled in the art would glean from disclosure that the inventors possessed the claimed invention with the negative limitation at the time of filing. Applicant states that the instant cloning system is an improvement over known systems without using Cre-lox and cites Figures 1 and 2 and the working examples on pages 8-11. Applicant also states there is only a discussion of the

drawbacks using the Cre-lox system in the disclosure. Applicant concludes that the skilled artisan would clearly recognize that loxP is not part of the invention.

Applicant's arguments and a review of the case laws cited have been fully considered, but are found unpersuasive in view of the teachings in the specification. The case cited by applicant, *Eiselstein v. Frank*, does not apply to the circumstances in the instant case since the crux of the arguments in the law is centered on whether there was adequate written description for an approximate percentage range of a nickel alloy disclosed in a grandparent application. The negative limitation added to the instant claims has no previous or current basis for support. The written description section of *In re Kaslow* cited by applicant, also has no bearing on the instant rejections because it appears that the preferred embodiments of the invention were outlined broadly by the terms "check" and its implied meaning "audit", which was ultimately found unsupported in the original disclosure. The instant negative limitation can have no other implied meaning other than ultimate exclusion, which is not supported by the instant specification.

In response to *In re Wright*, cited by Applicant, it is fully agreed by the Examiner that *ipsis verbis* support for claim language is not required in a disclosure so long as the claimed concepts and limitations are fully supported by the originally filed specification. The case law of *In re Wright* is drawn to whether the negative limitation added to the claims, "not permanently fixed" was adequately described in the specification as originally filed. Adequate written description was found in the case law because the disclosure taught that the particles were never fixed to the surface due to the specific steps in the process and the examples emphasized the importance of not disturbing the particles, which indicated that they were not permanently fixed.

There is no such for support for the newly added negative limitation of plasmids that lack a loxP sequence either explicitly or implied.

Although *Ex Parte Grasselli*, cited by the Office, is not a lengthy case, it bears significance to the written description and new matter rejections in the instant case because of parallel circumstances. Claim 1 reproduced in the case law on page 394 specifies that sulfur, halogen, uranium, or the co-presence of vanadium and phosphorus are expressly excluded from the process. The court found that these negative limitations newly presented in the claims did not appear in the specification as filed and introduced new concepts. The instantly presented claims recite a new, negative limitation that specifically excludes "a loxP sequence" in the shuttle and backbone plasmids. As in the case of *Ex Parte Grasselli*, this negative limitation is not supported by the original disclosure. Although the instant figures and working examples on pages 8-11 do not use loxP sequences, the prohibitive use of these sequences in the plasmids is not conveyed. Support for other embodiments encompassed by the disclosure but not specifically discussed is found on page 11, lines 13-21 and page 16, lines 25-30. Specifically, the disclosure states on page 11, lines 14-17, that "...numerous other possible backbone and shuttles will be apparent to those of skill in the art...[I]n light of the techniques disclosed herein and the general recombinant techniques known in the art...". The disclosure teaches conventional recombinant techniques for the propagation of adenoviruses and since loxP is a well known recombinant technique in the art, the scope of the mechanisms for using this technique is not limited. The specification does not convey prohibitive or detrimental effects for using this sequence in the instant plasmids. The drawbacks for using the Cre-lox recombinase system, discussed by Applicant above, are found in the disclosure page 3, lines 5-9. The

invention is based on homologous recombinant methods well practiced in the art and the instant disclosure also discusses the disadvantages of using these, see page 2, lines 16 to page 3, line 9. The disclosure does not convey the prohibitive or exclusionary use of employing the loxP sequence commonly used homologous recombination techniques in the instant disclosure. Therefore, it is determined that the specification does not convey that the inventors had basis for the negative limitation in the invention at the time of filing and the added phrase constitutes new matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 4, 5, 10, 11, and 13-25 rejected under 35 U.S.C. 103(a) as being unpatentable over Aoki et al. (Molecular Medicine. 1999; 5: 224-231) and Chinnadurai et al. (Journal of Virology. 1979; 32 (2): 623-628) for reasons of record.

Applicant argues that Chinnadurai et al. differs from the claimed invention in a few respects. First, the method of Chinnadurai et al. uses cotransfection of parental DNA fragments with overlapping sequences to generate infectious virus. Second, low levels of adenovirus were produced as a result of incomplete digestion. Third, the reference teaches that propagating recombinant adenovirus is impractical with different infectious virions and intact DNAs because the recombinants cannot be distinguished from the parental plaques.

Applicant's arguments have been considered, but are found unpersuasive. The asserted divergence in the teachings of Chinnadurai et al. are not different from the claimed invention and actually lend themselves to arriving at the invention instantly claimed. The instant invention also uses overlapping parental fragment sequences, i.e., map units 9.2 to 16.1 in the same homologous recombination technique taught by Chinnadurai et al. Also, since Chinnadurai et al. teaches pitfalls to avoid, such as selecting an inefficient enzyme for digestion and using intact DNAs when using a homologous recombination method, the ordinary artisan is aware of the importance of using a more efficient enzyme and smaller DNA fragments. With respect to the infectivity of the adenovirus generated by Chinnadurai et al. and the lack of such in the instant invention, Chinnadurai et al. teaches the generation of several non-infectious mutants, see the first sentence of the second column on page 625 of Chinnadurai and the first sentence of the second column on page 224 of Aoki et al. If the reference taught every element in the claims, the reference would have been considered under 35 U.S.C. § 102. In addition, the 6.9 map unit region instantly taught to facilitate the homologous recombination step overlaps with the map units used in the method of Chinnadurai et al. and is not out of scope with the teachings of the disclosure, see page 11, lines 14-17.

Applicant also argues that Aoki et al. teaches that map units 9.2-16.1 are not sufficient to generate adenovirus and recites a passage derived from the Results section on page 226. Applicant further asserts that Aoki et al later discounts the role of map units 9.2 to 16.1 in the shuttle plasmid because they are left out of Figure 1A. Applicants also argue that Aoki et al. uses the Cre-loxP system to generate recombinant adenovirus in mammalian cells, even having known about the method of Chinnadurai et al.

In response, it is determined that the teachings of Aoki et al. have been misinterpreted. The title under the Results section on page 226 is "Strategy to Make Adenovirus Using Cre-loxP System In Vitro". Therefore, it is Aoki et al. teaches making recombinant adenovirus with a shuttle plasmid comprising Ad map units 0-1 and 9.2 to 16.1 and a gene of interest an adenovirus backbone plasmid lacking map units 0-9.2 starting with the lefthand ITR. Aoki et al. teaches "Cre recombinase produces the full-length recombinant adenoviral vector in vitro by *intermolecular recombination between the loxP sites and these two linearized molecules*". (Emphasis added.) Therefore, Aoki et al. teaches direct homologous recombination between the loxP sites and the overlapping parental fragments consisting of map units 9.2 to 16.1 are critical for homologous recombination to occur to generate adenovirus. Both the shuttle plasmid and the adenovirus backbone contain these overlapping segments in Aoki et al. and it is known from the teachings of Chinnadurai et al., and Aoki et al., that non-infectious adenovirus is generated by overlapping parental fragments. Further, it is conceded that Aoki et al. used the Cre-loxP system in view of the teachings of Chinnadurai et al. However, both methods rely on the same mechanism to mediate homologous recombination between two directly repeated sites to generate non-infectious adenovirus clones.

Applicant argues that impermissible hindsight reasoning is used to arrive at the present invention and further argues that there is no suggestion in the prior art to combine the references.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the

time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). The reference of Aoki et al. teaches a method of generating recombinant adenoviruses with two components with overlapping sequences. Aoki et al. also references the teachings of Chinnadurai et al., recounting knowledge commonly known in the art.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, motivation is derived from the innate desire of everyone skilled in the art to generate non-infectious adenovirus in a time-efficient manner. Fewer steps are involved for making recombinant adenoviruses by the method of Chinnadurai et al. Motivation to incorporate the specific components comprising particular map units taught by Aoki et al. into the method of Chinnadurai et al. is established by the success of Aoki et al. in producing non-infectious adenovirus with a limited number of specific overlapping map units that are recombined. Further, one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation to produce the claimed invention since homologous recombination is the mechanism used in both Aoki et al. and Chinnadurai et al. Therefore, the invention as a whole

would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Claims 2, 3, and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aoki et al. and Chinnadurai et al. as applied to claims 4, 5, 10, 11, and 13-25 above, and further in view of Krougliak et al. (Human Gene Therapy. 1995; 6: 1575-1586) for reasons of record.

Applicant asserts that Krougliak et al. does not remedy the deficiencies of Aoki et al. and Chinnadurai et al. Specifically, the reference deletes E1, E4, and protein IX to make more room for gene insertions and that both Aoki et al. and Krougliak et al. make a recombinant adenovirus when the genome contains map units 0-1 and the lefthand ITR in the cell.

Applicant's arguments have been considered, but are found unpersuasive because the claims rendered obvious by the teachings of Krougliak et al. in view of Aoki et al. and Chinnadurai et al. are drawn to modifying E3 and E4. The adenovirus vectors of Krougliak et al. are only used to show motivation for deleting adenovirus regions since other ingredients and limitations in the claims, such as the left hand ITR, have been rendered obvious.

Claims 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aoki et al., Chinnadurai et al., and Krougliak et al. as applied to claims 2-6, 10, 11, and 13-25 above, and further in view of Breakfield et al. (5,965,441) for reasons of record.

Applicant argues that the Office uses hindsight to arrive at the Applicant's invention and states that the combination of references would yeild an adenovirus with loxP, AAV/HSV hybrid sequences, and the left-hand ITR.

In response, to the argument drawn to hindsight reasoning, conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on

obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). As discussed above, the combined teachings of Aoki et al. and Chinnadurai et al. render the incorporation of cre-lox obsolete and the teachings of Breakfield are incorporated to show motivation to add an HSV amplicon to Aoki's backbone plasmid.

Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Aoki et al. and Chinnadurai et al. as applied to claims 4, 5, 10, 11, and 13-25 above, and further in view of Chartier et al. (Journal of Virology. 1996; 70 (7): 4805-4810) for reasons of record.

Applicant argues that there is a lack of motivation to combine the references and that if all the references were combined, one would have an Ad vector comprising a loxP sequence and PacI sites of Chartier et al.

Applicant's arguments have bee fully considered as well as a review of the references, but are found unpersuasive. As discussed above, the combined teachings of Aoki et al. and Chinnadurai et al. render the incorporation of cre-lox obsolete and the teachings of Chartier et al. are incorporated to show motivation and success in incorporating the PacI sites in the shuttle plasmid of Aoki et al. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4426 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

SAF
Shanon Foley/SAF
June 5, 2002

James C. Housel
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